REMARKS/ARGUMENTS

The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter. Applicants believe that the current amendments place all claims in *prima facie* condition for allowance or, at least, in a better form for consideration on appeal. Accordingly, the consideration and entry of the present amendment after final rejection is respectfully requested.

Prior to the present amendment, claims 58-65 and 68-75 were pending in this application. With this amendment, Claims 58-60 and 71-73 have been canceled without prejudice and Claims 61, 62, 69, 74 and 75 have been amended to remove the dependence upon canceled claims.

Claims 61-65, 68-70, and 74-75 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants acknowledge the withdrawal of the rejections under 35 U.S.C. §112, second paragraph, and the enablement rejections under 35 U.S.C. §112, first paragraph. The remaining rejections under 35 U.S.C. §112, first paragraph for alleged lack of written description and under 35 U.S.C. §102 and §103 are addressed below.

I. Information Disclosure Statement

Applicants thank the Examiner for considering the information disclosure statement submitted on September 13, 2005.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62 and 69-75 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. The Examiner asserts that "[t]he specification does not provide sufficient written description as to the structural features of the claimed genus of PRO337 polypeptides and the correlation between the structure and function of the genus of PRO337 polypeptides, such as structural domains or motifs that are conserved or essential for activity and could distinguish members of the genus from those excluded." (Page 4 of the instant Office Action).

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Applicants submit that Claims 58-60 and 71-73 have been canceled; hence the rejection as it pertains to these claims is moot.

Applicants further submit that Examples 126 and 116 of the present application provide protocols for the chondrocyte re-differentiation assay and the proliferation of rat utricular supporting cells assay, respectively. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO337 polypeptide meets the limitations of the claims in that it induces chondrocyte re-differentiation or induces proliferation of rat utricular supporting cells. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8), including a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether a variant PRO337 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

The Examiner asserts that "[a]n adequate written description of a chemical invention requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed." (Page 5 of the instant Office Action). In support of this assertion, the Examiner cites *Univ. of Rochester v. G. D. Searle & Co.*

The case of *Rochester* is not parallel to the instant situation, as *Rochester* involved a situation in which functional limitations alone, without any structural limitations, were ruled insufficient to provide adequate written description. In *Rochester*, the claims were to inhibitor compounds. The protein to be inhibited was described, and a specific assay for screening compounds including peptides, polynucleotides, and small organic molecules for inhibitory activity was provided, but not a single example of an inhibitor was provided. Thus the recited functional limitation did not provide sufficient guidance as to which of the vast universe of peptides, polynucleotides and small organic molecules might possibly have inhibitory activity. While the instant claims also have a structural limitation, in that the claimed variants must have at least 95% sequence identity to the reference sequence of SEQ ID NO:523, the claims in *Rochester* were limited solely by the function of the desired sequence or compound. In the instant case the recited functional limitations supplement the recited structural limitations rather than substituting for them.

The Examiner further asserts that "[w]hen an inventor is unable to envision the detailed constitution of a polypeptide so as to distinguish it from other materials, as well as a method of obtaining it, conception is not achieved until reduction to practice has occurred, i.e., until after the polypeptide has been isolated." (Pages 5-6 of the instant Office Action). In support of this assertion, the Examiner cites *Burroughs Wellcome Co. v. Barr Laboratories Inc.* The Examiner made a similar assertion in the previous Office Action, stating that "the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation" (Pages 12-13 of the instant Office Action). In support of this assertion, the Examiner cited the cases of *Fiers v. Revel* and *Amgen v. Chugai.* (Page 5 of the Office Action mailed June 20, 2005).

Applicants submit that *Burroughs Wellcome* addressed conception in the context of methods of treating AIDS patients with AZT, and did not speak to conception of polypeptides. Applicants further submit that *Fiers v. Revel* and *Amgen v. Chugai* addressed conception and the written description requirement in the context of DNA-related inventions. The *Amgen* court held that conception of a DNA invention "has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated." 927 F.2d 1200 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991), at 1206. The *Fiers* court extended this decision into the written description arena, holding that "[i]f a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity." *Fiers*, 984 F.2d at 1171. Since the instant claims are directed to polypeptides, *Fiers* and *Amgen* are distinguished on the facts and do not apply.

More recently, in *Enzo Biochem., Inc. v. Genprobe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002), the court adopted the standard that "the written description requirement can be met by 'showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324. While the invention in *Enzo* was still a DNA, the holding has been treated as being applicable to proteins as well. Indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids.

Accordingly, current applicable case law holds that biological sequences are not adequately described **solely** by a description of their desired functional activities. The instant claims meet the standard set by the *Enzo* court in that the claimed sequences are defined not only by functional properties, but also by structural limitations. It is well established that a **combination** of functional and structural features may suffice to describe a claimed genus. "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[1] As discussed above, Applicants have recited structural features, namely, 95% sequence identity to SEQ ID NO:523, which are common to the genus. The genus of claimed polypeptides is further defined by having a specific activity for the polypeptide, wherein said polypeptide induces chondrocyte re-differentiation, or wherein said polypeptide induces proliferation of rat utricular supporting cells. Accordingly, a description of the claimed genus has been achieved.

This particular combination of functional activity and structural homology, as disclosed in the specification, has been recognized by the USPTO as sufficient to describe a claimed genus of polypeptides. The Examiner's attention is respectfully directed to Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence.

As discussed above, the procedures for making the claimed variant polypeptides are well known in the art and described in the specification. The specification also provides assays, shown in Example 116 and Example 126, for detecting the recited functional activities of the variant polypeptides. Finally, the claimed variant polypeptides possess both the specified

[1] M.P.E.P. §2163 II(A)(3)(a)

functional activity and a defined degree of sequence identity to the reference sequence, SEQ ID NO:523. Accordingly, the claimed polypeptide variants meet the standards set forth in the Written Description Guidelines.

Thus the specification provides adequate written description for polypeptides having at least 95% identity to SEQ ID NO:523 wherein said polypeptide induces chondrocyte re-differentiation, or wherein said polypeptide induces proliferation of rat utricular supporting cells. Applicants therefore respectfully request that the Examiner reconsider and withdraw the written description rejection of Claims 61-62, 69-70, and 74-75 under 35 U.S.C. §112, first paragraph.

III. Claim Rejections Under 35 U.S.C. §102

Claims 58-61 and 71-74 remain rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Struyk *et al.* (The Journal of Neuroscience, 15(3):2141-2156, March 1995). Struyk *et al.* teach an isolated polypeptide having 91% amino acid sequence identity with SEQ ID NO:523, and having 97% amino acid sequence identity with the polypeptide of SEQ ID NO:523 lacking its associated signal peptide.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Applicants submit that Claims 58-60 and 71-73 have been canceled; hence the rejection as it pertains to these claims is moot. Further, Claims 61 and 74, as amended herein, do not recite polypeptides having at least 95% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:523, lacking its associated signal peptide. Thus Struyk *et al.* does not anticipate the claims, as Struyk *et al.* does not disclose polypeptides having at least 95% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:523, or having at least 99% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:523, lacking its associated signal peptide.

Accordingly, withdrawal of the 35 U.S.C. §102(b) rejection over Struyk *et al.* is respectfully requested.

IV. Claim Rejections Under 35 U.S.C. §103

Claims 58-61 and 69-74 remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Struyk *et al.* in view of Grose (U.S. Patent No. 5,710,248, issued January 20, 1998). Struyk *et al.* teach an isolated polypeptide having 91% amino acid sequence identity with SEQ ID NO:523, and having 97% amino acid sequence identity with the polypeptide of SEQ ID

NO:523 lacking its associated signal peptide. Grose teaches a peptide tag for immunopurification and immunoprecipitation.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Applicants submit that Claims 58-60 and 71-73 have been canceled; hence the rejection as it pertains to these claims is moot. Further, Claims 61 and 74, as amended herein, do not recite polypeptides having at least 95% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:523, lacking its associated signal peptide. Thus Struyk *et al.* does not anticipate the claims, as this reference does not disclose polypeptides having at least 95% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:523, or having at least 99% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:523, lacking its associated signal peptide. Grose does not cure the deficiencies of Struyk *et al.*, as the teachings of Grose are limited to polypeptide tags. Thus Applicants respectfully submit that the instant claims are not obvious over Struyk *et al.* in view of Grose.

Accordingly, withdrawal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C12**).

Respectfully submitted,

Date: January 11, 2006

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